

**WHAT IS CLAIMED AS NOVEL & UNOBVIOUS  
IN UNITED STATES LETTERS PATENT IS:**

1. An oligonucleotide (oligo) that is anti-sense to an initiation codon, a coding region, a 5' or 3' intron-exon junction, an intron, a region within 2 to 10 nucleotides of the 5'-end and the 3'-end or a border section between a coding and non-coding region of a nucleic acid target comprising a gene(s) selected from interleukin-4 receptor, interleukin-5 receptor, CCR1, CCR3, Eotaxin-1, RANTES, MCP4, CD23, ICAM, VCAM, tryptase a, tryptase b, PDE4 A, PDE4 B, PDE4 C or PDE4 D gene; or anti-sense to their corresponding mRNAs; or pharmaceutically and veterinarily acceptable salts of the oligo(s); and optionally a surfactant that may be operatively linked to the oligo(s).

2. The oligo of claim 1, wherein the oligo is anti-sense to SEQ ID NOS: 1-2499.

3. The oligo of claim 1, wherein the oligo is anti-sense to at least two genes or RNAs.

4. The oligo of claim 1, wherein at least one mononucleotide is substituted or modified by one or more of phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, 3'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, boranophosphate, morpholino, siloxane, sulfide, sulfoxide, sulfone, formacetyl, thioformacetyl, methylene formacetyl, thioformacetyl, alkene, sulfamate, methyleneimino, methylenehydrazino, sulfonate, sulfonamide, amide, thioether, carbonate, carbamate, sulfate, sulfite, hydroxylamine, methylene(methylimino), methyleneoxy (methylimino), 2'-O-methyl, or phosphoramidate residues, or combinations thereof.

5. The oligo of claim 4, wherein all mononucleotides are substituted or modified.

6. The oligo of claim 1, wherein at least one mononucleotide is substituted or modified at the 2' position by one or more of OH, F, O-, S-, N-alkyl, O-alkyl-O-alkyl, N-alkenyl, N-alkynyl,  $O[(CH_2)_n O]_m CH_3$ ,  $O(CH_2)_n OCH_3$ ,  $O(CH_2)_2 ON(CH_3)_2$ ,  $O(CH_2)_n NH_2$ ,  $O(CH_2)_n CH_3$ ,  $O(CH_2)_n ONH_2$ , or  $O(CH_2)_n ON[(CH_2)_n CH_3]_2$ , wherein n or m are from 1 to about 10, C<sub>1</sub> to C<sub>10</sub> lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, SH, SCH<sub>3</sub>, OCN, Cl, Br, CN, CF<sub>3</sub>, OC<sub>3</sub>, SOCH<sub>3</sub>, SO<sub>2</sub> CH<sub>3</sub>, ONO<sub>2</sub>, NO<sub>2</sub>, N<sub>3</sub>, NH<sub>2</sub>, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, poly-alkylamino, or substituted silyl.

7. The oligo of claim 6, wherein all mononucleotides are substituted or modified.

8. The oligo of claim 1, wherein at least one mononucleotide is substituted or modified by one or more of 5-methylcytosine (<sup>14</sup>C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl adenine, 6-methyl guanine, 2-propyl adenine, 2-propyl guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, 5-halocytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil adenine, 8-halo adenine, 8-amino adenine, 8-thiol adenine, 8-thioalkyl adenine, 8-hydroxyl adenine, 8-halo guanine, 8-amino guanine, 8-thiol guanine, 8-thioalkyl guanine, 8-hydroxyl guanine, 5-bromo uracil, 5-trifluoromethyl uracil, 5-bromo cytosine, 5-trifluoromethyl cytosine, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 2-aminopropyladenine, 5-propynyluracil, 5-propynylcytosine or 5-methylcytosine.

9. The oligo of claim 8, wherein all mononucleotides are substituted or modified.

10. The oligo of claim 1, wherein a methylated cytosine (<sup>m</sup>C) is substituted for an unmethylated cytosine (C) in at least one CpG dinucleotide if present in the oligo(s).

11. The oligo of claim 1, wherein if the oligo contains adenosine (A), at least one A is substituted by a universal base selected from heteroaromatic bases that bind to a thymidine base but have antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors, or heteroaromatic bases that have no activity or have agonist activity at the adenosine A<sub>2a</sub> receptor.

12. The oligo of claim 11, wherein substantially all As are substituted by a universal base (s) selected from heteroaromatic bases that bind to a thymidine base but either have antagonist activity or less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors, or heteroaromatic bases that have no activity or have agonist activity at the adenosine A<sub>2a</sub> receptor

13. The oligo of claim 11, wherein the heteroaromatic bases are selected from pyrimidines or purines that may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH, or branched or fused primary or secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, or arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary or tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl or heteroaryl.

14. The oligo of claim 13, wherein the pyrimidines are substituted at a 1, 2, 3, and/or 4 position, and the purines are substituted at a 1, 2, 3, 4, 7 and/or 8 position.

15. The oligo of claim 13, wherein the pyrimidines or purines are selected from theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline or xanthine.

16. The oligo of claim 11, wherein the universal base is selected from 3 – nitropyrrole-2'-deoxynucleoside, 5-nitroindole, 2-deoxyribosyl-(5-nitroindole), 2- deoxyribofuranosyl – (5 – nitroindole), 2' – deoxyinosine, 2' – deoxynebularine, 6H, 8H – 3, 4 – dihydropyrimido [4, 5 – c] oxazine – 7 – one or 2 – amino – 6 – methoxyaminopurine.

17. The oligo of claim 1, wherein the oligo consists of up to about 10% A.

18. The oligo of claim 17, wherein the oligo consists of up to about 5% A.

19. The oligo of claim 18, wherein the oligo consists of up to about 3% A.

20. The oligo of claim 19, wherein the oligo is A-free.

21. The oligo of claim 1, wherein the nucleic acid is linked to an agent that enhances cell internalization or up-take and/or a cell targeting agent.

22. The oligo of claim 21, wherein the cell internalization or up-take enhancing agent comprises transferrin, asialoglycoprotein or streptavidin.

23. The oligo of claim 21, wherein the cell targeting agent comprises a vector, and the nucleic acid is operatively linked to the vector.

24. The oligo of claim 23, wherein the vector comprises a prokaryotic or eukaryotic vector.

25. A composition comprising the oligonucleotide of claim 1, and a pharmaceutically or veterinarily acceptable carrier or diluent and optionally therapeutic agents.

26. The composition of claim 25, wherein the carrier or diluent comprises gaseous, liquid or solid carrier or diluent.

27. The composition of claim 25, wherein the therapeutic agents comprise surfactants, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, antioxidants, flavoring agents, propellants or preservatives.

28. The composition of claim 27, wherein the surfactants are lipid or non-lipid surfactants.

29. The composition of claim 28, wherein the surfactants comprises surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D, surfactant protein E, active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, artificial lamellar bodies vehicles for surfactant components, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, polyoxy ethylene 23 lauryl ether (Brij 35<sup>®</sup>), t-octyl phenoxy polyethoxy ethanol (Triton X-100<sup>®</sup>), dipalmitoyl phosphatidyl choline (DPPC), phosphatidyl glycerol (PG) (ALEC<sup>®</sup>), tyloxapol (Exosurf<sup>®</sup>), surfactant-associated proteins (Survanta<sup>®</sup>) or C<sub>22</sub>H<sub>19</sub>C<sub>10</sub> (Atovaquone<sup>®</sup>).

30. The composition of claim 27, wherein the RNA inactivating agent comprises an enzyme.

31. The composition of claim 30, wherein the enzyme comprises a ribozyme.

32. The composition of claim 25, further comprising a propellant.

33. The composition of claim 1, wherein the oligo is present in an amount of about 0.01 to about 99.99 w/w of the composition.

34. A formulation comprising the composition of claim 25, wherein the carrier comprises a hydrophobic carrier.

35. The formulation of claim 34, selected from intrabuccal, intrapulmonary, respirable, nasal, inhalable, intracavitary, intraorgan, or slow release formulations.

36. The formulation of claim 34, wherein the carrier is selected from a solid or liquid carrier.

37. The formulation of claim 34, which comprises a sprayable or aerosolizable powder, solution, suspension or emulsion.

38. The formulation of claim 34, which comprises a sprayable or aerosolizable aqueous or alcoholic solution or suspension, oily solution or suspension, or oil-in-water or water-in-oil emulsion.

39. A capsule or cartridge, comprising the formulation of claim 34.

40. The formulation of claim 34, which comprises a formulation of particle size about  $0.5\mu$  to about  $10\mu$ , or about  $10\mu$  to about  $500\mu$ .

41. The formulation of claim 34, which comprises a nasal formulation of particle size about  $10\mu$  to about  $500\mu$ .

42. The formulation of claim 34, which is a respirable or inhalable formulation comprising a solid powdered or liquid aerosol or spray of particle size about  $0.5\mu$  to about  $10\mu$ .

43. The formulation of claim 34, in bulk, or in single or multiple unit dose form.

44. A vector, comprising the oligonucleotide of claim 1.

45. A cell, comprising the oligonucleotide of claim 1.

46. A diagnostic or therapeutic kit for delivery of an oligonucleotide(s) (oligo(s)) comprising, in separate containers,  
the delivery device;  
the composition of claim 25; and

instructions for loading the composition into the device and for its use.

47. The kit of claim 46, wherein the delivery device comprises a nebulizer, a dry powder inhaler, a pressurized inhaler or insufflator.

48. The kit of claim 46, wherein the delivery device delivers single metered doses.

49. The kit of claim 46, wherein the delivery device is adapted for receiving and piercing or opening a capsule(s), blister(s) or cartridge(s) and producing a solid powdered or liquid aerosol or spray.

50. The kit of claim 46, wherein the composition is in an inhalable, respirable, nasal, intracavitary, intraorgan or intrapulmonary formulation.

51. The kit of claim 46, wherein the composition is of particle size about  $0.5\mu$  to about  $10\mu$ , or about  $10\mu$  to about  $500\mu$ .

52. The kit of claim 48, wherein the composition is provided in a pierceable or openable capsule, blister or cartridge.

53. The kit of claim 48, comprising the delivery device, a surfactant, the composition and other therapeutic agents.

54. The kit of claim 48, further comprising a solvent selected from organic solvents or organic solvents mixed with one or more co-solvents.

55. A method for reducing or inhibiting expression of a gene or mRNA encoding interleukin-4 receptor, interleukin-5 receptor, CCR1, CCR3, Eotaxin-1, RANTES, MCP4, CD23, ICAM, VCAM, tryptase a, tryptase b, PDE4 A, PDE4 B, PDE4 C or PDE4 D, comprising contacting the oligonucleotide of claim 1 with cells or tissues, under conditions effective for hybridization, and allowing hybridization to occur, whereby expression is reduced or inhibited.

56. The method of claim 55, wherein the hybridization is conducted under stringent condition in vitro.

57. The method of claim 55, wherein the hybridization is conducted under semi-stringent condition in vitro.

58. The method of claim 55, wherein the hybridization is conducted under physiological condition in vivo.

59. A method for preventing or treating a respiratory or lung disease, comprising administering to the airways of a subject an effective amount of an inhibitor of one or more nucleic acid target(s) or expressed product(s) thereof comprising a gene(s) selected from interleukin-4 receptor, interleukin-5 receptor, CCR1, CCR3, Eotaxin-1, RANTES, MCP4, CD23, ICAM, VCAM, tryptase a, tryptase b, PDE4 A, PDE4 B, PDE4 C or PDE4 D.

60. The method of claim 59, wherein the inhibitor is administered intrapulmonary, intraorgan, intracavitarily, intrabuccally, intranasally, by inhalation or into the subject's respiratory system.

61. The method of claim 59, wherein the inhibitor is the composition of claim 25.

62. The method of claim 61, wherein the composition comprises solid powdered or liquid particles of about 0.5 to about 10  $\mu$  in size.

63. The method of claim 61, wherein the composition is administered as powdered solid or liquid particles of about 10  $\mu$  to about 500  $\mu$  in size.

64. The method of claim 59, wherein the composition further comprises other therapeutic agents.

65. The method of claim 64, wherein the therapeutic agent(s) comprise(s) anti-adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor agents or adenosine A<sub>2a</sub> receptor stimulating agents other than the nucleic acid(s).

66. The method of claim 59, further comprising administering a surfactant.

67. The method of claim 66, wherein the surfactant comprises lipid or non-lipid surfactant.

68. The method of claim 59, wherein the respiratory or lung disease comprises asthma, bronchoconstriction, impeded respiration, cystic fibrosis (CF), Chronic Obstructive Pulmonary Diseases (COPD), allergic rhinitis (AR), Acute Respiratory Distress Syndrome (ARDS), pulmonary hypertension and bronchitis.

69. The method of claim 59, wherein the the respiratory or lung disease is associated with hyper-responsiveness to and/or increased levels of, adenosine and/or levels of adenosine (A) receptor(s), and/or asthma and/or lung allergy(ies) and/or lung inflammation.

70. The method of claim 59, wherein the hyper-responsiveness to, or increased levels of, adenosine, levels of adenosine (A) receptor(s), and/or bronchoconstriction, and/or asthma, and/or lung allergy(ies) and/or lung inflammation is(are) associated with inflammation or an inflammatory disease.

71. The method of claim 60, wherein the subject is a mammal.

72. The method of claim 71, wherein the mammal is a human or a non-human mammal.

73. The method of claim 61, wherein the composition is administered in an amount of about 0.005 to about 150 mg/kg body weight.

74. The method of claim 73, wherein the composition is administered in an amount of about 0.01 to about 75 mg/kg body weight.

5 75. The method of claim 74, wherein the composition is administered in an amount of about 1 to about 50 mg/kg body weight.

76. The method of claim 59, which is a prophylactic or therapeutic method.

10 77. The method of claim 59, wherein the oligo is obtained by  
(a) selecting fragments of a target nucleic acid having at least 4 contiguous bases consisting of G or C; and  
(b) obtaining a second oligo 4 to 60 nucleotides long comprising a sequence that is anti-sense to the selected fragment.

15 78. The method of claim 59, wherein the oligo consists of up to about 10% A.

79. The method of claim 78, wherein the oligo consists of up to about 5% A.

20 80. The method of claim 79, wherein the oligo consists of up to about 3% A.

81. The method of claim 80, wherein the oligo is A-free.

25 82. The method of claim 59, wherein the inhibitor is selected from dansylcadaverin, glycylamide, methylamine, n-propylamine, n-hexylamine, bacitracin, ethylamine, t-butylamine, an antibody to the expressed product or the oligo of claim 1, or combination thereof.

83. The method of claim 59, further comprising administering a subject of interest with one or more anti-asthma agent(s).

30 84. The method of claim 82, wherein the oligo is anti-sense to at least two genes, ESTs or RNAs.

85. A use of the oligonucleotide of claim 1 for production of a medicament for the prevention and/or treatment of a respiratory or lung disease.

35 86. The use of claim 85, wherein the respiratory or lung disease comprises airway inflammation, allergy(ies), asthma, impeded respiration, cystic fibrosis (CF), Chronic Obstructive Pulmonary Diseases (COPD), allergic rhinitis (AR), Acute Respiratory Distress Syndrome (ARDS), pulmonary hypertension, lung inflammation, bronchitis, airway obstruction, or bronchoconstriction.

40 87. A method for screening a candidate compound for the prevention and/or treatment of a respiratory or lung disease that binds to one or more nucleic acid target(s) or expressed product(s) thereof comprising a gene(s)

selected from interleukin-4 receptor, interleukin-5 receptor, CCR1, CCR3, Eotaxin-1, RANTES, MCP4, CD23, ICAM, VCAM, tryptase a, tryptase b, PDE4 A, PDE4 B, PDE4 C or PDE4 D.

5           88.     The method claim 87, wherein the the nucleic acid target(s) or their expressed product(s) is(are) in a purified form from the expression system.

          89.     The method of claim 88, wherein the expressed product(s) is(are) expressed in or on the cell.

          90.     The method of claim 87, wherein the binding is detected by a label.

10           91.     The method of claim 87, wherein the candidate compound suppresses the expression of one or more nucleic acid target(s).

          92.     The method of claim 87, wherein further comprising steps of contacting a candidate compound with or  
15    introducing into a cell expressing the one or more nucleic acid target(s) or their expressed product(s), and detecting the suppression, reduction or inhibition of their expression.

          93.     The method of claim 92, wherein the suppression, reduction or inhibition is detected by measuring the  
20    level of the transcribed mRNA of the genes.

          94.     The method of claim 92, wherein the cell comprises a construct comprising a nucleic acid target that is  
linked to a reporter gene system in a cell